

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Nienaber, *et al.*

Serial No.:

Filed: August 7, 2001

For: LIGAND SCREENING AND  
DESIGN BY X-RAY  
CRYSTALLOGRAPHY

Examiner: J. Weber

Group Art Unit: 1651

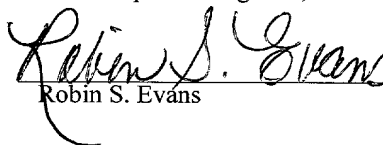
Case No.: 6308.US.D1

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**PRELIMINARY AMENDMENT**

Dear Sir:

In conjunction with the filing of the subject divisional application of U.S. Serial No. 09/263,904, now pending, please enter the following amendments to the claims prior to examination thereof:

**IN THE CLAIMS:**

Please cancel claims 1-15 and add new claims 36-44, as follows:

36. (New) A process for identifying a ligand which binds to a target biomolecule comprising the steps of:
- a) obtaining a target biomolecule crystal and the X-ray diffraction pattern of said target biomolecule;
  - b) exposing the target biomolecule crystal to a mixture of at least two potential ligands and obtaining an X-ray crystal diffraction pattern therefrom; and
  - c) determining whether a ligand/target biomolecule complex is formed by comparing the X-ray crystal diffraction patterns of said target biomolecule crystal when exposed to said mixture of said at least two potential ligands to the X-ray diffraction pattern of said target biomolecule crystal obtained when not exposed to said mixture of said at least two potential ligands.
37. (New) The process according to Claim 36 further comprising the step of converting said target biomolecule diffraction patterns into electron density maps using known phases of said target biomolecule crystal and comparing said electron density maps of said target biomolecule crystals without exposure to said mixture and with exposure to said mixture to determine whether a ligand/target biomolecule complex is formed.
38. (New) The process according to Claim 36 wherein the target biomolecule is exposed to said mixture by soaking the target biomolecule crystal in a solution containing said mixture.
39. (New) The process according to Claim 36 wherein said ligands in said mixture are diversely shaped at the molecular level.
40. (New) The process according to Claim 36 wherein at least one of the ligands in said mixture is a biologically-active moiety.
41. (Amended) The process according to Claim 36, wherein the target biomolecule is a polypeptide.

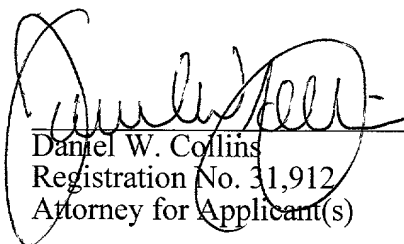
42. (Amended) The process according to Claim 36, wherein the target biomolecule is other than a native polypeptide.
43. (New) A biologically active moiety identified by the process according to claim 40.
44. (New) The process according to Claim 36 wherein at least one of said ligands in said mixture is a lead compound.

Remarks

In view of the subject Preliminary Amendment, Applicants respectfully submit that the present application is in condition for allowance and allowance thereof is respectfully requested.

Respectfully submitted,  
Nienaber, *et al.*

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